PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 37/02, C07K 7/10

A1

(11) International Publication Number: WO 89/ 03686

(43) International Publication Date: 5 May 1989 (05.05.89)

(21) International Application Number: PCT/GB88/00877

(22) International Filing Date: 20 October 1988 (20.10.88)

(31) Priority Application Number: 8724564

(32) Priority Date: 20 October 1987 (20.10.87)

(33) Priority Country: GB

(71) Applicant *(for all designated States except US)*: CELLTECH LIMITED [GB/GB]; 216 Bath Road, Slough, Berkshire SL1 4EN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : RIDDELL, Alistair, James [GB/GB]; 'Kia Ora', lymington Bottom, Four Marks, Alton, Hampshire GU34 5AH (GB). EDWARDS, Christopher, Richard, Watkin [GB/GB]; 'Innerwick', 2 Ellersley Road, Edinburgh EH12 6HZ (GB).

(74) Agent: HALLYBONE, Huw, George; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).

(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: CGRP FOR CEREBRAL BLOOD SUPPLY IMPROVEMENT

(57) Abstract

A new medical use for calcitonin gene-related peptide (CGRP) is disclosed. The use of CGRP for the treatment of deficiencies in cerebral blood supply is described. The cerebral blood supply may become deficient for a number of reasons such as in the body's natural response to cerebral bleeding. CGRP is described as being particulary useful in the treatment of subarachnoid haemorrhage.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	ML	Mali
AU	Australia	GA	Gabon	MR	Mauritania
BB	Barbados	GB	United Kingdom	MW	Malawi
BE	Belgium	HU	Hungary	NL	Netherlands
BG	Bulgaria	IT	Italy	NO	Norway
BJ	Benin	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SN	Senegal
CH	Switzerland	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
DE	Germany, Federal Republic of	LU	Luxembourg	TG	Togo
DK	Denmark	MC	Monaco	US	United States of America
FI	Finland	MG	Madagascar		

CGRP for cerebral blood supply improvement.

Field of the Invention

This invention relates to a new medical use for certain compounds and pharmaceutical compositions containing them. In particular it relates to the use of calcitonin gene-related peptide (CGRP) in treatment of deficiencies in cerebral blood supply.

Background to the Invention

Calcitonin gene-related peptide is a product of the calcitonin gene expression system. Alternative processing of RNA transcribed from the calcitonin gene leads to the production in neuronal tissue of CGRP, a 37 amino acid peptide. CGRP has been discovered in a number of species including rats, chickens and humans. The CGRPs are a very closely related group of compounds differing from each other by no more than a few amino acids. To date CGRP has been described as being principally of use in the treatment of hypertension owing to its properties on the cardiovascular system where it has been found to cause vasodilatation and to lower blood pressure. CGRP has also been postulated to play a role in calcium regulation and gastric acid secretion. We have now discovered that CGRP is useful in the treatment of deficiencies in cerebral blood supply.

The cerebral blood supply may become deficient for a number of reasons including, for example, cerebrovascular spasm. Cerebrovascular spasm of the carotid artery is the body's natural response to cerebral bleeding, cutting off the blood supply to the brain. Cerebral haemorrhage such as subarachnoid haemorrhage has many causes including the rupture of weakened blood vessels within the brain and mechanical damage to the head (trauma). Unless the blood supply and hence oxygen supply to the brain is restored the cerebrovascular spasm normally leads to brain damage and sometimes to death.

The blood supply to the brain is also deficient in cases of stroke due either to infarction, i.e. occlusion of the cerebral blood vessel, or to rupturing of the blood vessel resulting in cerebral haemorrhage.

The cerebral blood supply is also interrupted during a migraine attack and by restoring cerebral blood supply it is therefore possible to alleviate the symptoms of the migraine attack.

We have now found that CGRP is useful in the treatment of deficiencies in the cerebral blood supply in human subjects.

Summary of the Invention

Accordingly in a first aspect the invention provides CGRP for use in the treatment of a deficiency in cerebrovascular blood supply.

In order to be useful in the treatment of deficiencies in cerebral blood supply it is essential that the therapeutic agent is able to selectively affect the cerebrovascular bed, such that the blood supply is increased at the desired site. A further essential requirement is that the blood supply should be increased without substantially lowering the blood pressure. Current therapeutic strategies to reverse constriction of cerebral blood vessels are unsatisfactory because they also result in lowering of blood pressure, so exacerbating the original problem. Hitherto, therefore, there has been a real need for an effective treatment for restoring cerebral blood flow and/or reversing cerebral vasospasm. We have found that it is possible to achieve both the required selectivity of site of action and the desired increase in cerebral blood supply without substantially affecting blood pressure, by administration of an appropriate amount of CGRP.

As used herein the term CGRP, in addition to naturally occurring CGRPs, includes also biologically active fragments, analogues and derivatives thereof which have the characteristic cerebrovascular blood supply affecting properties of CGRP; i.e. which preferentially act on the cerebrovascular bed to differentially increase cerebral blood supply without substantially affecting blood pressure. The CGRPs, fragments, analogues and derivatives may be naturally occurring or may be produced chemically e.g. by chemical modification, cleavage, or synthesis or they may be produced by employing recombinant DNA techniques. The fragments,

analogues and derivatives may include non-peptide compounds as well as peptide compounds. The CGRP may comprise an animal CGRP, e.g. rat or chicken CGRP, though is preferably human calcitonin gene-related peptide (hCGRP). Human calcitonin gene-related peptide exists in at least two forms known as alpha hCGRP, for instance as described in US Patent No. 4549986, and beta hCGRP, for instance as described in published European Patent Application No. EP 188400A. As used herein, the term 'hCGRP' is used to denote α- and β- hCGRP. The use of α- hCGRP is especially preferred.

CGRP is particularly useful in the treatment of deficiencies in cerebrovascular blood supply in human subjects such as are associated with subarachnoid haemorrhage, stroke, trauma and migraine.

According to a second aspect of the invention we provide a method of treatment of a human subject suffering from a deficiency in cerebrovascular blood supply which comprises administering an effective amount of CGRP to the subject.

Typically the amount of CGRP used is an amount of CGRP which is effective to differentially increase cerebrovascular blood supply without substantially affecting blood pressure.

In a third aspect the invention provides a pharmaceutical composition comprising CGRP for use in the treatment of a deficiency in cerebrovascular blood supply.

In a fourth aspect the invention provides a pharmaceutical composition in unit dosage form, each unit dose comprising an amount of CGRP which acts to differentially increase cerebrovascular blood supply without substantially affecting blood pressure in combination with a pharmaceutically acceptable carrier, excipient or diluent.

The pharmaceutical composition according to the fourth aspect of the invention preferably contains 0.01 to 45μg CGRP, preferably 0.08μg to 35μg CGRP, more preferably from 5 to 35μg CGRP and most preferably from 5 to 25μg CGRP.

In a fifth aspect the invention provides a process for the production of a pharmaceutical composition according to the fourth aspect of the invention comprising bringing into association with a pharmaceutically acceptable carrier, excipient or diluent, aliquot amounts of CGRP sufficient to differentially increase cerebrovascular blood supply without substantially affecting blood pressure to provide unit doses.

In a sixth aspect the invention provides the use of an amount of CGRP which acts to differentially increase cerebrovascular blood supply without substantially affecting blood pressure for the manufacture of a medicament for the treatment of a deficiency in cerebrovascular blood supply.

In a seventh aspect the invention provides a drug for therapy of deficiencies in cerebral blood supply comprising a CGRP as an active ingredient.

In an eighth aspect, the invention provides a cerebral blood supply improver comprising CGRP.

In a ninth aspect, the invention provides a method for the treatment of deficiencies in cerebral blood supply which comprises administering to a patient a GCRP.

Pharmaceutical compositions for use according to the present invention may be formulated in conventional manner, optionally with one or more physiologically acceptable carriers diluents or excipients.

Compounds for use according to the present invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for nasal administration or administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such

as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents; emulsifying agents; non-aqueous vehicles; and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The CGRP may be formulated for parenteral administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The CGRP may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the CGRP may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodi- fluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispenser device may be accompanied by instructions for administration.

The dose at which CGRP will be administered to man will be such that the cerebral blood supply is differentially increased and blood pressure is not substantially affected. The precise dose of CGRP will depend upon the route of administration, the potency of the CGRP and the body weight and pathology of the patient. The important factor is believed to be the concentration of CGRP which is present at the target vascular bed. On an individual patient basis the dose of the CGRP which should be administered to cause the desired effect may be determined by administering a low dose of CGRP for 10-20 minutes and then increasing the dose every 10-20 minutes until the desired effect is seen. A CGRP may be administered to an average 70kg man by IV infusion at doses in the range 0.01-32ng/kg/min, preferably in the range 0.06 to 24ng/kg/min, more preferably in the range 4 to 24ng/kg/min, and most preferably in the range 4-16ng/kg/min. For example, α-CGRP and β-CGRP may be administered to an average 70kg man by IV infusion at doses in the range 4ng/kg/min to 16ng/kg/min over a time period of 20 minutes. In some cases it may be desirable to infuse the patient with CGRP for longer time periods e.g. for up to or greater than 1 hour or for more than 24 hours.

CGRP for use in the present invention may be obtained using recombinant DNA technology as described in British Patent No. 2141430B and published European Patent Application No. EP-A-188400. Alternatively the CGRP may be produced by chemical synthesis using conventional techniques well knwon in the art, see for example published European Patent Application No. EP-A-188400.

CGRP is particularly useful in the treatment of deficiencies in cerebral blood supply since it shows the desired profile of activity i.e. it selectively affects the cerebrovascular bed without substantially affecting blood pressure.

The CGRP may be tested for its ability to differentially increase cerebrovascular blood supply in animals and humans using the Doppler technique as described in the examples hereinafter. The effect of the CGRP on blood pressure may be measured using conventional techniques.

Brief Description of Drawings

The differential increase in cerebrovascular blood supply affected by CGRP and CGRP analogues has been demonstrated in human volunteers and in rats respectively, using the Doppler technique as described below and, with reference to the accompanying Figures in which:

Figure 1 is a histogram showing the effect of administration of hCGRP and glyceryl trinitrate (GTN) on systolic blood pressure in humans,

Figure 2 is a histogram showing the effect of administration of hCGRP and GTN on diastolic blood pressure in humans,

Figure 3 is a histogram showing the effect of administration of hCGRP and GTN on heart rate in humans,

Figure 4 is a histogram showing the effect of administration of hCGRP and GTN on velocity of blood flowing through the internal carotid artery in humans,

Figure 5 is a histogram showing the effect of administration of hCGRP and GTN on velocity of blood flowing through the common carotid artery in humans,

Figure 6 is a histogram showing the effect of administration of hCGRP and GTN on velocity of blood flowing through the renal artery in humans,

Figure 7 is a histogram showing the effect of administration of hCGRP and GTN on velocity of blood flowing through the femoral artery in humans,

Figure 8 shows a graph of cardiovascular responses to CGRP analogue CB0011 infusion for 60 min in rats,

Figure 9 shows a graph of cardiovascular responses to CGRP analogue CB0010 infusion for 60 min in rats humans,

Figure 10 shows a graph of cardiovascular responses to CGRP analogue CB0009 infusion for 60 min in rats,

Figure 11 shows a graph of cardiovascular responses to CGRP analogue CB0008 infusion for 60 min in rats,

Figure 12 shows a graph of cardiovascular responses to CGRP analogue CB0007 infusion for 60 min in rats,

Figure 13 shows a graph of cardiovascular responses to CGRP analogue H7030 infusion for 60 min in rats

In figures 8 to 13 the following symbols denote dosage levels as indicated below

▲ = 0.006nmol/hr

○ = 0.06nmol/hr

● = 0.6nmol/hr

Description of Specific Embodiments

Example 1

The following example illustrates a pharmaceutical formulation containing α-hCGRP for use in the treatment of deficiencies in cerebrovascular blood supply.

Infusion	µg/dose
Active Ingredient	33.6µg
1% lactose	1ml

The active ingredient is dissolved in a solution of 1% lactose in distilled water and is then freeze dried. The freeze dried material is reconstituted in saline to the desired volume before intravenous administration.

Example 2

Study 1

Effect of CGRP on Cerebrovascular Blood Supply

The Doppler technique measures the velocity of blood passing through blood vessels and where the velocity of the blood flow is increased it is postulated that the blood supply to the organ supplied by the particular vessels is increased. The Doppler technique is therefore believed to provide an indirect measurement of blood supply.

Direct evidence of increased blood supply through the common carotid artery is seen by the facial flushing of human volunteers to whom CGRP has been administered.

Test Procedure

The study involved 10 young human male subjects each of whom underwent a detailed clinical and laboratory screening before recruitment. Each subject was involved on one study day with readings being taken within the following regime: baseline/drug/ recovery/lunch/baseline/drug/recovery.

During the drug period, subjects received in random order either α-hCGRP at a dose rate of 1.5 micrograms per minute by constant rate infusion or glyceryl trinitrate (GTN) sublingually in a dose necessary to induce a throbbing headache. The period of α-hCGRP infusion was generally between 20 and 40 minutes with a similar duration of recording time being applicable to the GTN phase of the study. At each of the recording periods measurements were made of blood pressure (using a semiautomated sphygmomanometer) heart rate (recorded from the same machine) and blood flow indices were recorded using a Doptek Duplex Centre. The blood flow indices were recorded in the internal carotid, common carotid, renal and femoral arteries. The indices used in the study were blood velocity (cm/sec) and the pulsatility index (PI):

$$PI = \frac{(\text{Systolic velocity}) - (\text{diastolic velocity})}{\text{Mean velocity}}$$

The PI gives a good indication of the overall velocity waveform. It is usually regarded as an index of downstream impedence to flow. However, when the vessel itself is being altered pharmacologically the PI will change in a direction dependent on various competing factors. Particularly, the systolic velocity (determined largely by the force of cardiac contraction) and the diastolic velocity (determined largely by the force of impedence) will determine the PI according to the ratio of their change. For example, if all that happens is a reduction in downstream impedence then the PI would fall. This would be the case with a "simple" vasodilator. However, if the speed of blood passing through the vessel during systole also increases then the PI might rise, as indeed was found in this study.

The mean results from the 10 subjects are shown in Figure 1 to 7.

RESULTS

1. Blood pressure: As can be seen from Figures 1 and 2, GTN significantly reduced both systolic and diastolic blood pressure, while α-hCGRP had no significant effect.
2. Heart rate: As can be seen from Figure 3, GTN produced a trend towards an increase in heart rate, but this was not significant. In contrast, α-hCGRP caused a striking tachycardia, despite the lack of hypotension.
3. Blood velocity: As can be seen from Figures 4 and 5, α-hCGRP increased blood velocity in both the internal and common carotid arteries. α-hCGRP had no effect on blood velocity in the renal and femoral arteries, as shown in Figures 6 and 7, and GTN did not influence velocity in any of these arteries.
4. Pulsatility Index: α-hCGRP increased the pulsatility index in only the internal carotid artery, which supplies the brain. GTN increased pulsatility index in only the common carotid artery, which also supplies the face.
5. Symptoms:
   (a) Facial flushing: All subjects became flushed following α-hCGRP and none following GTN.
   (b) Head swelling: Subjects experienced significantly more feelings of swelling following α-hCGRP than GTN as determined by a visual analogue scale. However, some degree of swelling was also noted following GTN as determined by this means.

Example 3

Study 2

Effect of α and β CGRP on Cerebrovascular Blood Supply

This was a single blind placebo-controlled rising dose study in a group of six healthy male volunteers. All subjects received placebo in the first period of the study. In periods 2 and 3 single

intravenous doses of α and β CGRP respectively were administered. There was an interval of at least seven days between successive doses to each subject.

Doses of 16ng/kg/min were administered at a rate of 0.5ml/minute for 20 minutes. After infusion 5-10ml saline were flushed through the infusion set.

Left ventricular function, and femoral and common, internal and external carotid blood flow were measured prior to dosing, 10 minutes after the start of the infusion and 30 minutes and 1 hour after the end of the infusion in each period of the study. Mean arterial pressure was measured before; during and after the end of the infusion.

The ventricular cardiac parameters measured were cardiac output in L/min and heart rate in BPM. Cardiac anatomical data were obtained from the real-time two dimensional ultrasound image, and velocity flow recorded with the sternal knotch area.

Measurements were made of mean blood velocity and mean blood flow in the common, internal and external carotid and in the femoral arteries. Identification of the anatomical site required and accurate positioning of the Doppler probe were confirmed each time with the Duplex system.

The mean results from a total of six volunteers are shown in Table 1.

The results show a stimulation of cardiac activity accompanied by an over supply of blood to the carotid blood vessels; without substantially affecting blood pressure.

SUBSTITUTE SHEET

PARAMETER	n = 6 α(16ng/kg/min)			n = 6 β(16ng/kg/min)			Placebo		
Post start of infusion	10'	30'	60'	10'	30'	60'	10'	30'	60'
Common carotid									
volume (ml/min)	+282	+164	+6.5	+273	+90	+0.5	-6.3	-36.7	-21.3
velocity (cm/sec)	+13	+7	+0.2	+12	+3.5	-0.3	-0.3	-3.0	-1.0
Internal Carotid									
volume (ml/min)	+185.2	+31.5	+15.7	+106.7	+58.5	+8.5	+8.8	+14.3	-1.5
velocity (cm/sec)	+8.2	+3.3	+0.0	+5.5	+3.3	+0.5	+0.67	+1.0	0.0
External Carotid									
volume (ml/min)	+177.3	+103.8	-5.7	+280	+116.5	+28.3	+8.6	+5.7	+4.5
velocity (cm/sec)	+13.2	+8.0	-0.8	+23	+9.5	+2.3	+1.0	+0.5	+0.3
Femoral									
volume (ml/min)	+99	+21	+0.3	+67	+6	-27	-36.2	-18.8	-20.5
velocity (cm/sec)	+3	+0.7	-0.2	+2	+0.2	-0.8	-1.2	-0.8	-0.7
Heart Rate	+14	+9	-0.2	+14	+6	+5	-3	-3.7	-7.5
Mean Arterial Pressure	-6	-10	-5	-6	-6	-7	-0.5	-3	-2
Cardiac Output	+2	+1.7	+0.9	+2.8	+1.3	+0.6	-0.1	-0.2	-0.2

Table 1

Example 4

Conscious, Wistar rats (n=8 in all groups) with renal, mesenteric and hindquarters flow probes, or with bilateral common carotid flow probes, were given CGRP analogues CB0007 and CB0008, or CB0009 and CB0011, or CB0010 and H7030 (structures given in Table 2). The animals were randomized to receive one of each pair of analogues on the first experimental day (the other analogue being given on the second experimental day) at doses of 0.006, 0.06 and 0.6nmol/hr for periods of 1 hour, separated by 1 hour post-infusion periods. The results are shown in Figures 8 to 13.

The CGRP analogues were synthesised using conventional peptide synthesis (see for example Merrifield R.B, Fed. Proc. Fed. Amer. Soc. Exp. Biol, 24 412 (1962)) following the FMOC procedure.

The experimental protocol ran over 2 days and animals were randomized to receive one of the following pairs of analogues on day 1:- CB0007 or CB0008; CB0009 or CB0011; CB0010 or H7030. On the second experimental day the remaining analogue of the pair was given. All analogues were dissolved in isotonic saline (containing 1% bovine serum albumin); the amount of lyophilizate dissolved was adjusted according to the stated peptide content, such that infusion of appropriately diluted solutions at a rate of 0.3ml/hr would deliver doses calculated to be 0.006, 0.06 or 0.6nmol/hr. Following a 30 min baseline period, infusions were given for 60 min, followed by a 60 min post-infusion period. All analogues were given in increasing doses to avoid any carry-over effects of the higher doses.

Measurements were made at -10, 0, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, and 120 min, with the infusion running between 0 and 60 min.

Table 2

ACDTATCVTH	RLAGLLSRSG	GVVKNNFVPT	NVGSKAF	α-CGRP
SCDTATCVTH	RLAGLLSRSG	GVVKNNFVPT	NVGSKAF	CB0009
ACDTATCVTH	RLAGLLSRSG	GVVKNNFVPT	NVGSEAF	CB0010
ACDTATCVTH	RLAGLLSRSG	GMVKNNFVPT	NVGSKAF	CB0007
ACDTATCVTH	RLAGLLSRSG	GMVKSNFVPT	NVGSKAF	CB0008
ACNTATCVTH	RLAGLLSRSG	GMVKNNFVPT	NVGSKAF	CB0011
ACNTATCVTH	RLAGLLSRSG	GVVKSNFVPT	NVGSKAF	H-7030

At a dose of 0.6nmol/hr all analogues caused tachycardia, hypotension and hindquarters and carotid hyperaemias. However, while the changes in heart rate and mean blood pressure were similar with all analogues, H7030 caused the numerically largest carotid hyperaemia, (as judged from the integrated, i.e., area-under-the-curve, response) and did so without compromising renal perfusion, althought there was a marked reduction in mesenteric blood flow.

At a dose of 0.06nmol/hr, analogues CB0007 and CB0008 (that were administered to the same animals), exerted significantly different carotid hyperaemic effects, with the latter analogue being more potent. Compound H7030 also had greater carotid hyperaemic effects than CB0007, and both CB0008 and H7030 exerted their enhanced carotid hyperaemic effects without influencing renal blood flow, whereas the latter variable was reduced in the presence of CB0007. Analogue CB0008 also caused a greater increase in carotid blood flow than did analogues CB0009 and CB0010.

At a dose of 0.006nmol/hr, analogue H7030 was the only one to cause an increase in heart rate.

The profile of activity of the CGRP analogues showing a selective effect on the carotids in rats supports their use in the treatment of deficiencies in cerebral blood supply in humans.

CLAIMS

1. CGRP for use in the treatment of a deficiency in cerebrovascular blood supply.

2. Human CGRP for use in the treatment of a deficiency in cerebrovascular blood supply.

3. H7030 for use in the treatment of a deficiency in cerebrovascular blood supply.

4. A CGRP according to claims 1 to 3 for use in the treatment of subarachnoid haemorrhage.

5. A CGRP according to Claims 1 to 3 for use in the treatment of migraine.

6. A method of treatment of a human subject suffering from a deficiency in cerebrovascular blood supply which comprises administering an effective amount of CGRP.

7. A pharmaceutical composition comprising CGRP for use in the treatment of a deficiency in cerebrovascular blood supply.

8. A pharmaceutical composition in unit dosage form, each unit dose comprising an amount of CGRP which acts to differentially increase cerebrovascular blood supply without substantially affecting blood pressure in combination with a pharmaceutically acceptable carrier, excipient or diluent.

9. A pharmaceutical composition according to Claim 8 comprising 0.01 to 45μg CGRP.

10. A pharmaceutical composition according to Claim 8 comprising 0.08 to 35μg CGRP.

11. A pharmaceutical composition according to Claim 8 comprising 5 to 35μg CGRP.

12. A pharmaceutical composition according to Claim 8 comprising 5 to 25μg CGRP.

13. A process for the production of a pharmaceutical composition according to Claim 8, comprising bringing into association with a pharmaceutically acceptable carrier, excipient or diluent, aliquot amounts of CGRP sufficient to differentially increase cerebrovascular blood supply without substantially affecting blood pressure to provide unit doses.

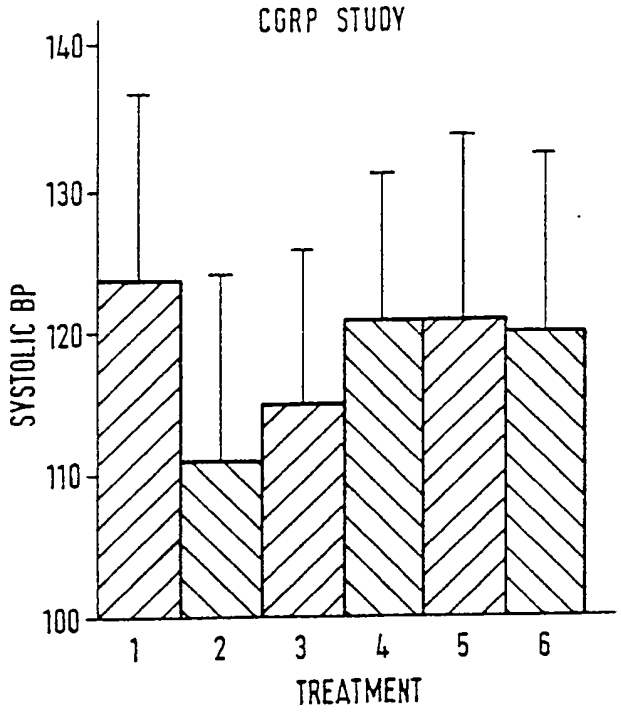
14. The use of an amount of CGRP which acts to differentially increase cerebrovascular blood supply without substantially affecting blood pressure for the manufacture of a medicament for the treatment of a deficiency in cerebrovascular blood supply.

15. A drug for therapy of deficiencies in cerebral blood supply containing a CGRP as an active ingredient.

16. A cerebral blood supply improver comprising CGRP.

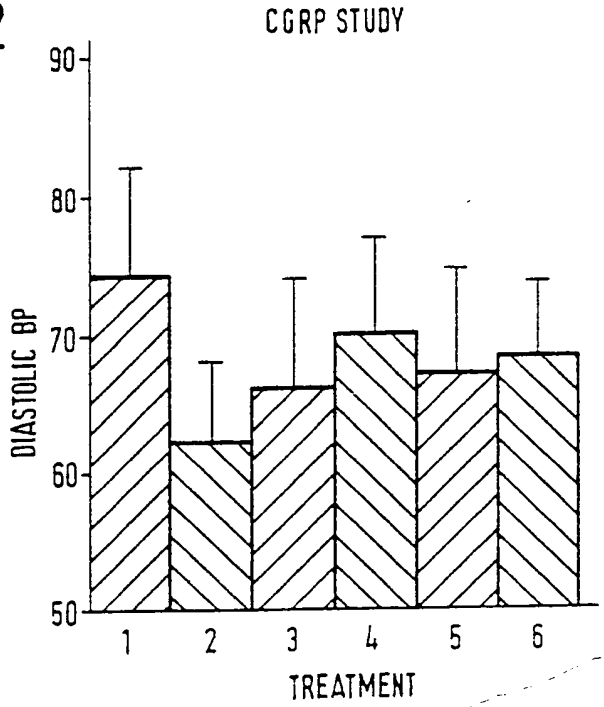
17. A method for the treatment of deficiencies in cerebral blood supply which comprises administering to a patient a CGRP.

FIG . 1



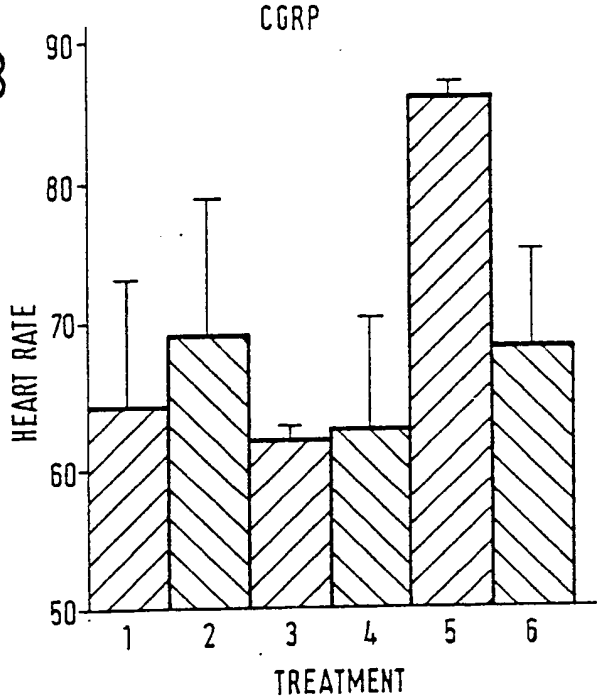
1:PREGTN 2.GTN 3.POSTGTN 4.PRECGRP 5.CGRP 6.POSTCGRP

FIG . 2



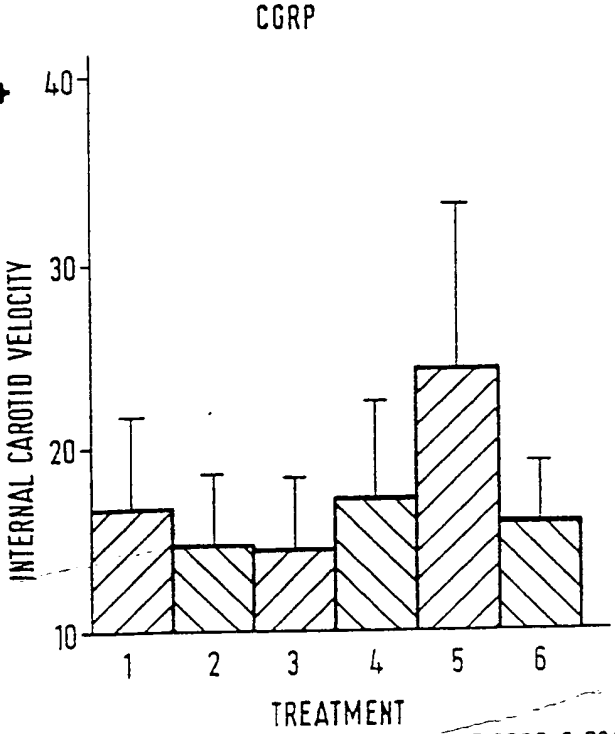
1. PREGTN 2.GTN 3.POSTGTN 4.PRECGRP 5.CGRP 6.POSTCGRP

FIG. 3



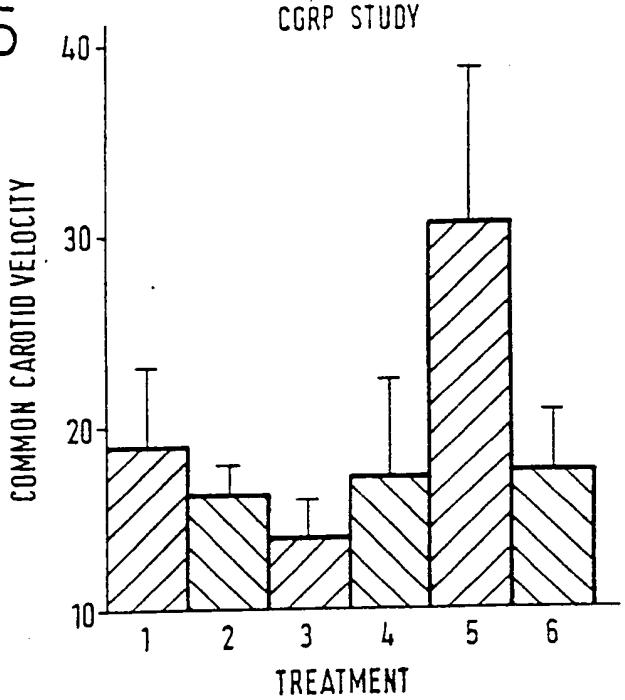
1. PREGTN 2. GTN 3. POSTGTN 4. PRECGRP 5. CGRP 6. POSTCGRP

FIG. 4



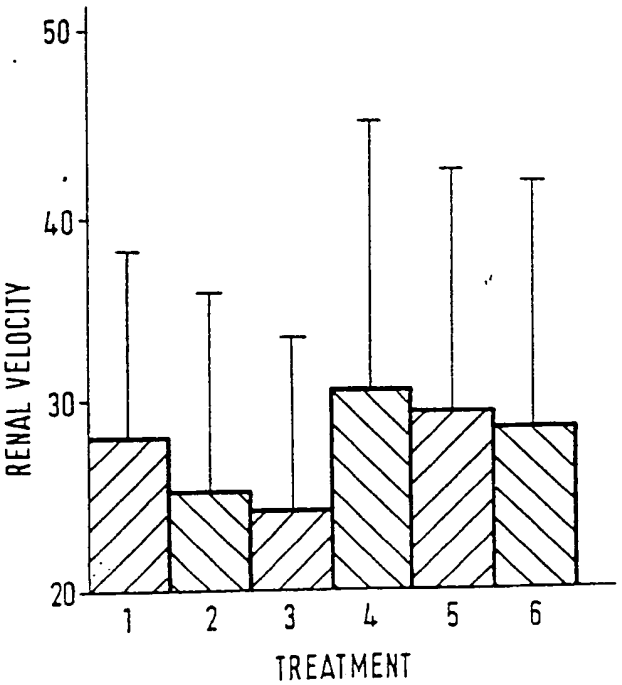
1. PREGTN 2. GTN 3. POSTGTN 4. PRECGRP 5. CGRP 6. POSTCGRP

FIG .5



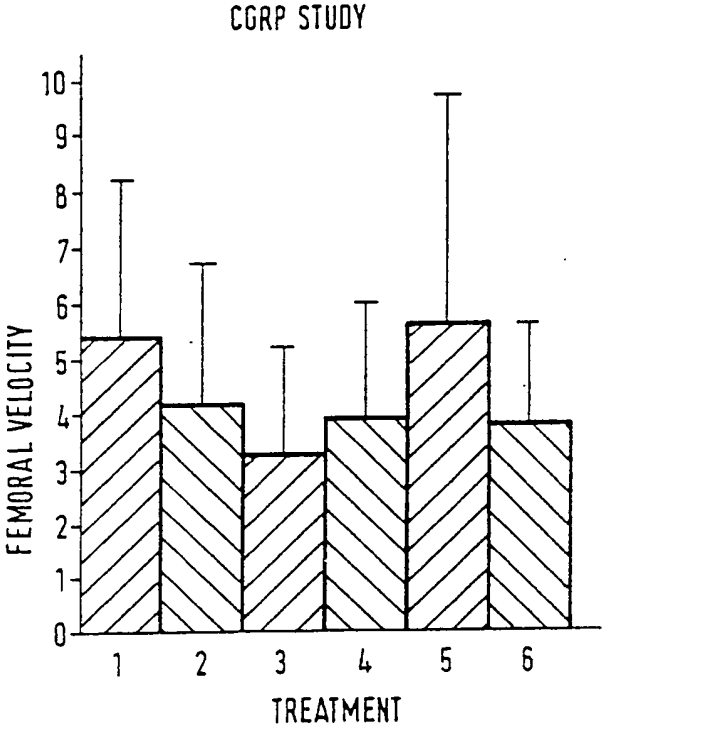
1. PREGTN 2. GTN 3. POSTGTN 4. PRECGRP 5. CGRP 6. POSTCGRP

FIG .6



1. PREGTN 2. GTN 3. POSTGTN 4. PRECGRP 5. CGRP 6. POSTCGRP

FIG. 7


CGRP STUDY
FEMORAL VELOCITY
0
1
2
3
4
5
6
7
8
9
10
1
2
3
4
5
6
TREATMENT
1.PREGTN 2.GTN 3.POSTGTN 4.PRECGRP 5.CGRP 6.POSTCGRP

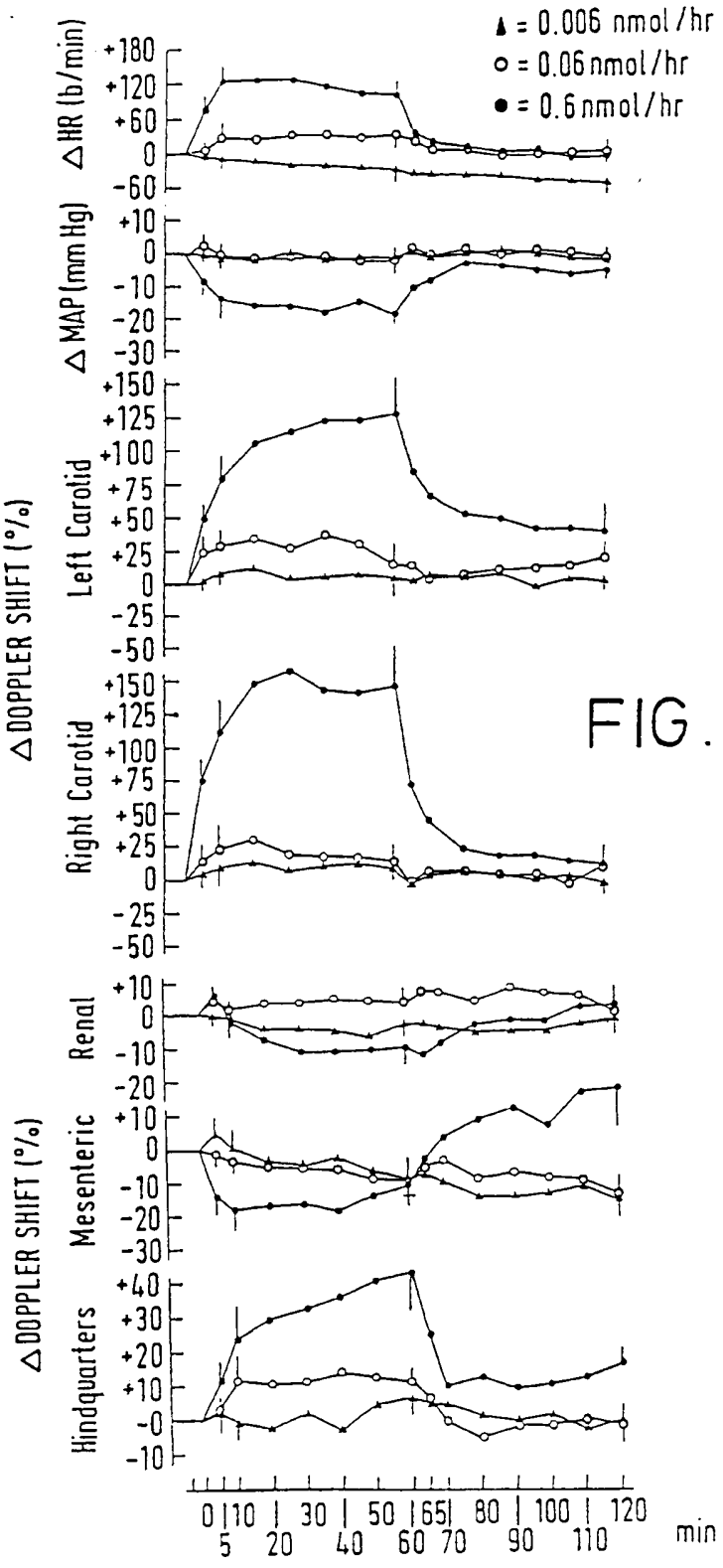

▲ = 0.006 nmol/hr
○ = 0.06 nmol/hr
● = 0.6 nmol/hr
Δ HR (b/min)
+180
+120
+60
0
-60
Δ MAP (mm Hg)
+10
0
-10
-20
-30
Δ DOPPLER SHIFT (%)
Left Carotid
+150
+125
+100
+75
+50
+25
0
-25
-50
Right Carotid
+150
+125
+100
+75
+50
+25
0
-25
-50
Renal
+10
0
-10
-20
Δ DOPPLER SHIFT (%)
Mesenteric
+10
0
-10
-20
-30
Hindquarters
+40
+30
+20
+10
-0
-10
0 10 30 50 65 80 100 120
5 20 40 60 70 90 110
min

FIG. 8

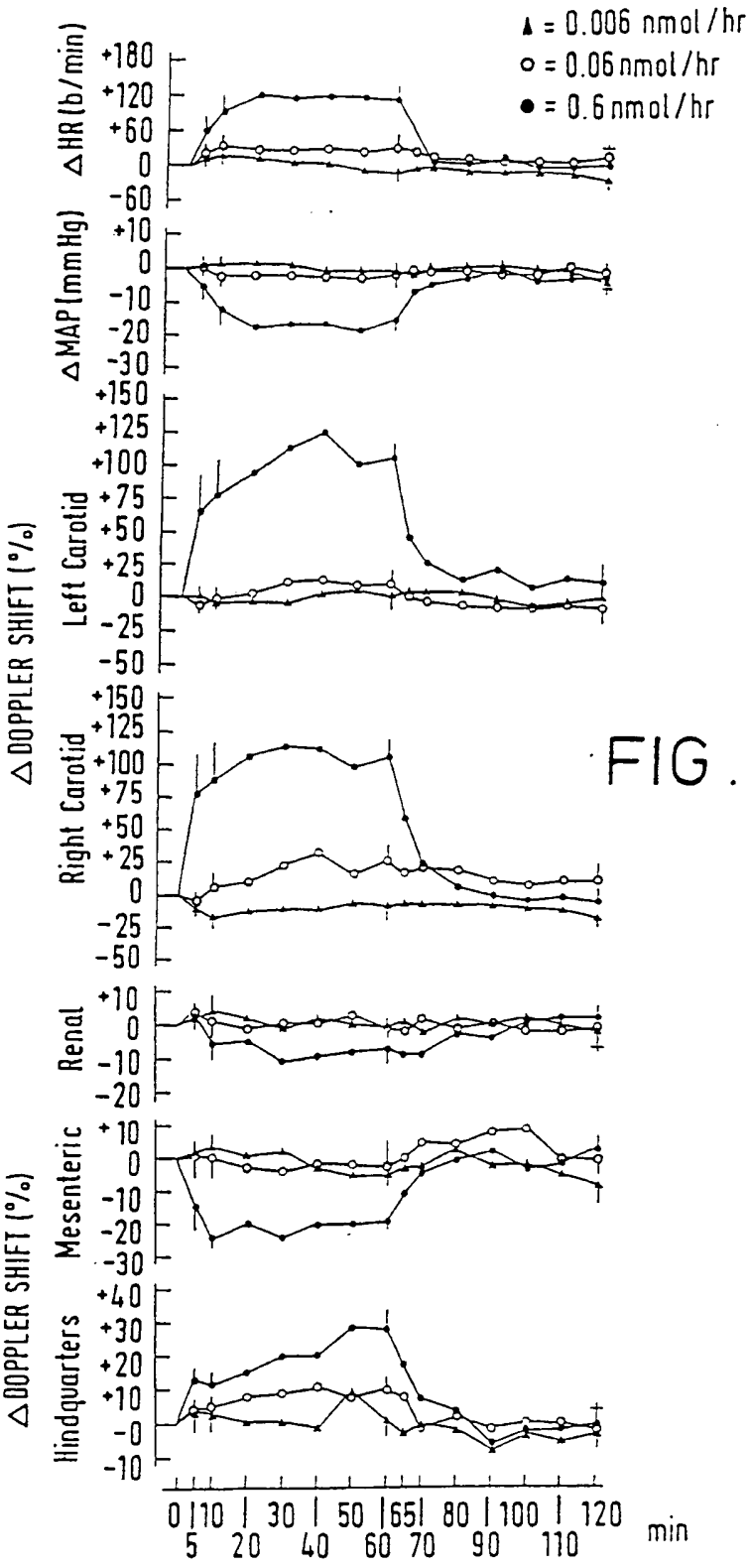

▲ = 0.006 nmol/hr
○ = 0.06 nmol/hr
● = 0.6 nmol/hr
ΔHR (b/min)
+180
+120
+60
0
-60
ΔMAP (mmHg)
+10
0
-10
-20
-30
Left Carotid
+150
+125
+100
+75
+50
+25
0
-25
-50
Right Carotid
Renal
Mesenteric
Hindquarters
+40
+30
+20
+10
-0
-10
ΔDOPPLER SHIFT (%)
0 | 10 | 30 | 50 | 65 | 80 | 100 | 120
5 20 40 60 70 90 110
min

FIG. 9

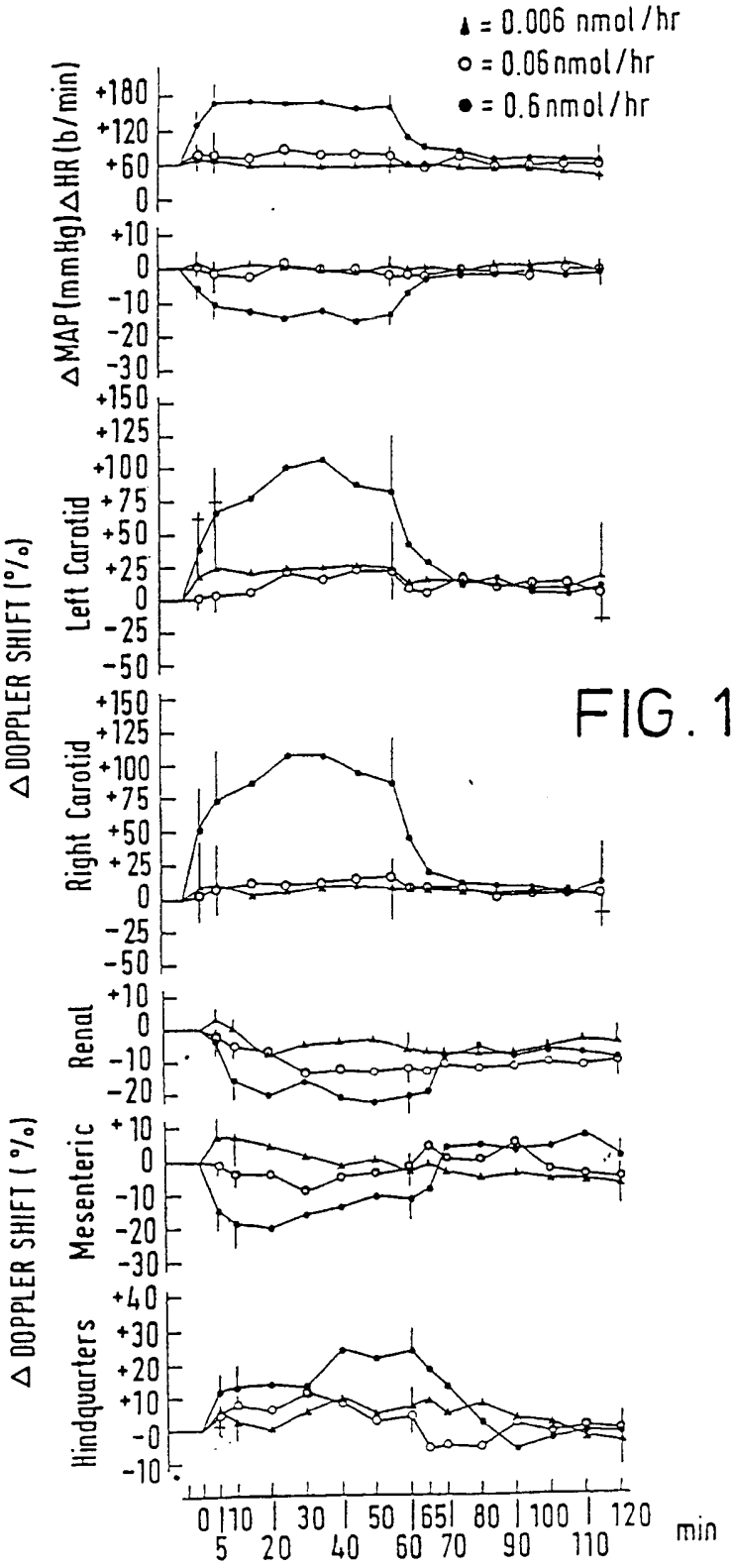

▲ = 0.006 nmol/hr
○ = 0.06 nmol/hr
● = 0.6 nmol/hr
Δ MAP (mm Hg) Δ HR (b/min)
+180
+120
+60
0
+10
0
-10
-20
-30
Δ DOPPLER SHIFT (%)
Left Carotid
+150
+125
+100
+75
+50
+25
0
-25
-50
Right Carotid
+150
+125
+100
+75
+50
+25
0
-25
-50
Renal
+10
0
-10
-20
Δ DOPPLER SHIFT (%)
Mesenteric
+10
0
-10
-20
-30
Hindquarters
+40
+30
+20
+10
-0
-10
0 10 30 50 65 80 100 120 min
5 20 40 60 70 90 110

FIG. 10

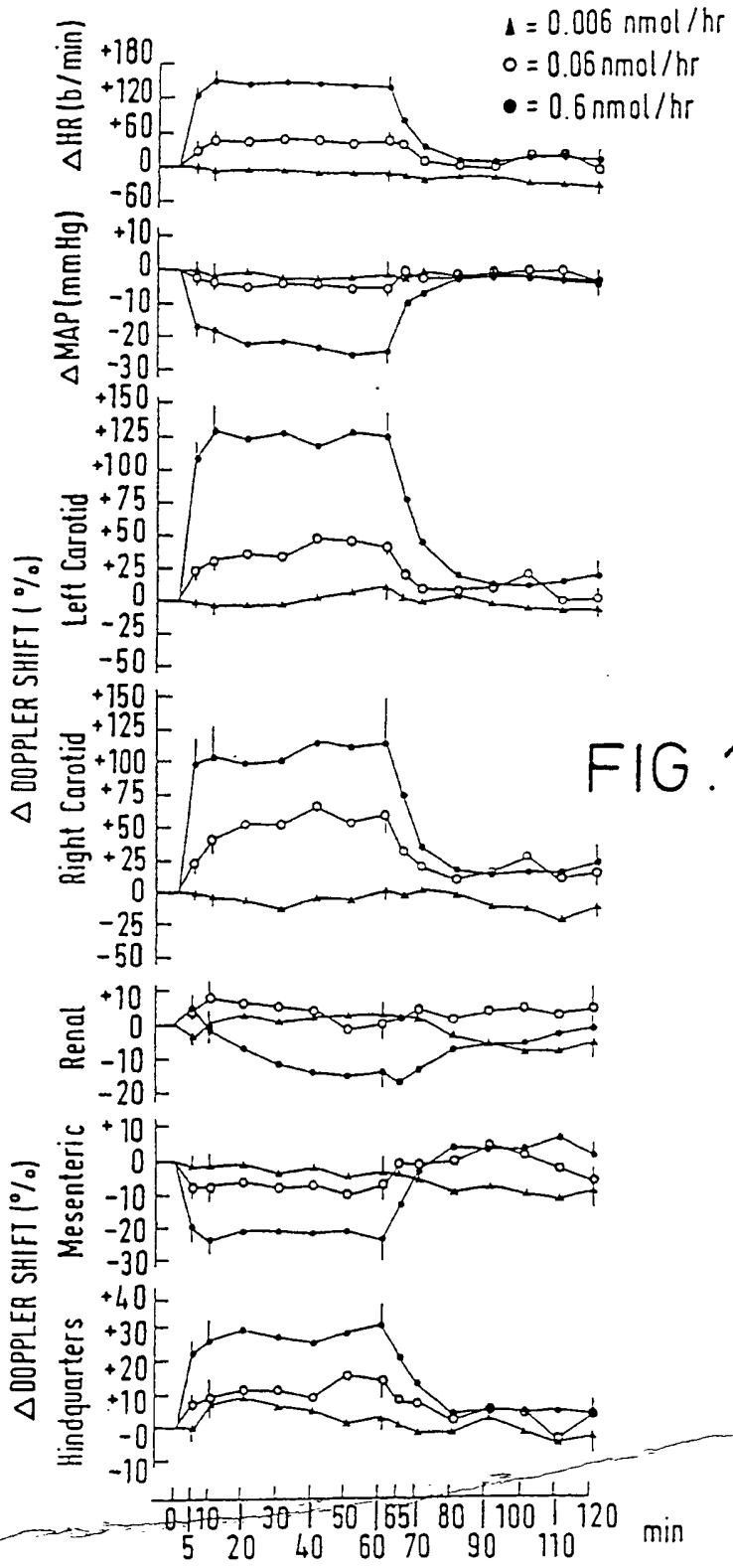

▲ = 0.006 nmol/hr
○ = 0.06 nmol/hr
● = 0.6 nmol/hr
ΔHR (b/min)
+180
+120
+60
0
-60
ΔMAP (mmHg)
+10
0
-10
-20
-30
Δ DOPPLER SHIFT (%)
Left Carotid
+150
+125
+100
+75
+50
+25
0
-25
-50
Right Carotid
Renal
Mesenteric
Δ DOPPLER SHIFT (%)
Hindquarters
+40
+30
+20
+10
-0
-10
0 10 30 50 65 80 100 120
5 20 40 60 70 90 110
min

FIG.11

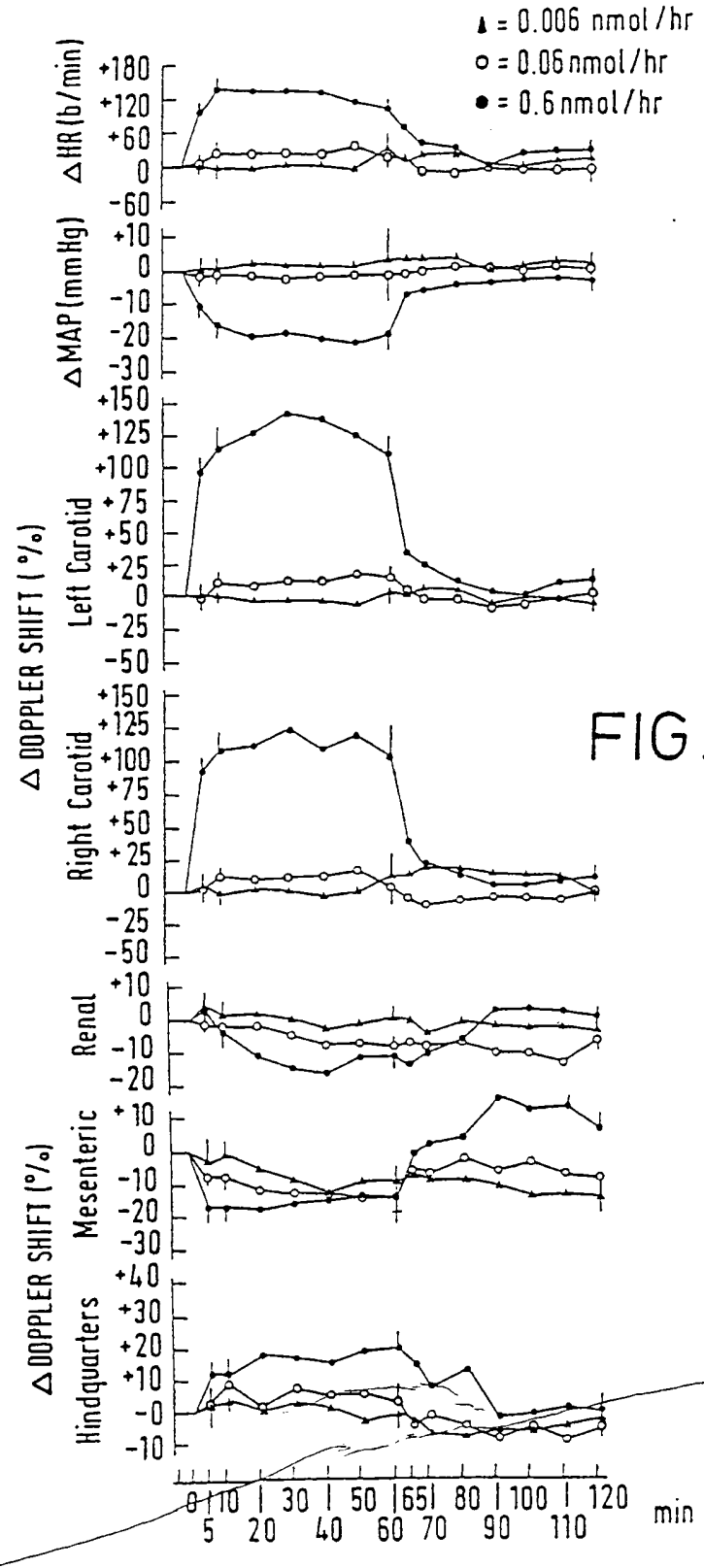

▲ = 0.006 nmol/hr
○ = 0.06 nmol/hr
● = 0.6 nmol/hr
ΔHR (b/min)
+180
+120
+60
0
-60
ΔMAP (mmHg)
+10
0
-10
-20
-30
Δ DOPPLER SHIFT (%)
Left Carotid
+150
+125
+100
+75
+50
+25
0
-25
-50
Right Carotid
Renal
Δ DOPPLER SHIFT (%)
Mesenteric
+40
+30
+20
+10
-0
-10
Hindquarters
0 10 30 50 65 80 100 120 min
5 20 40 60 70 90 110

FIG. 12

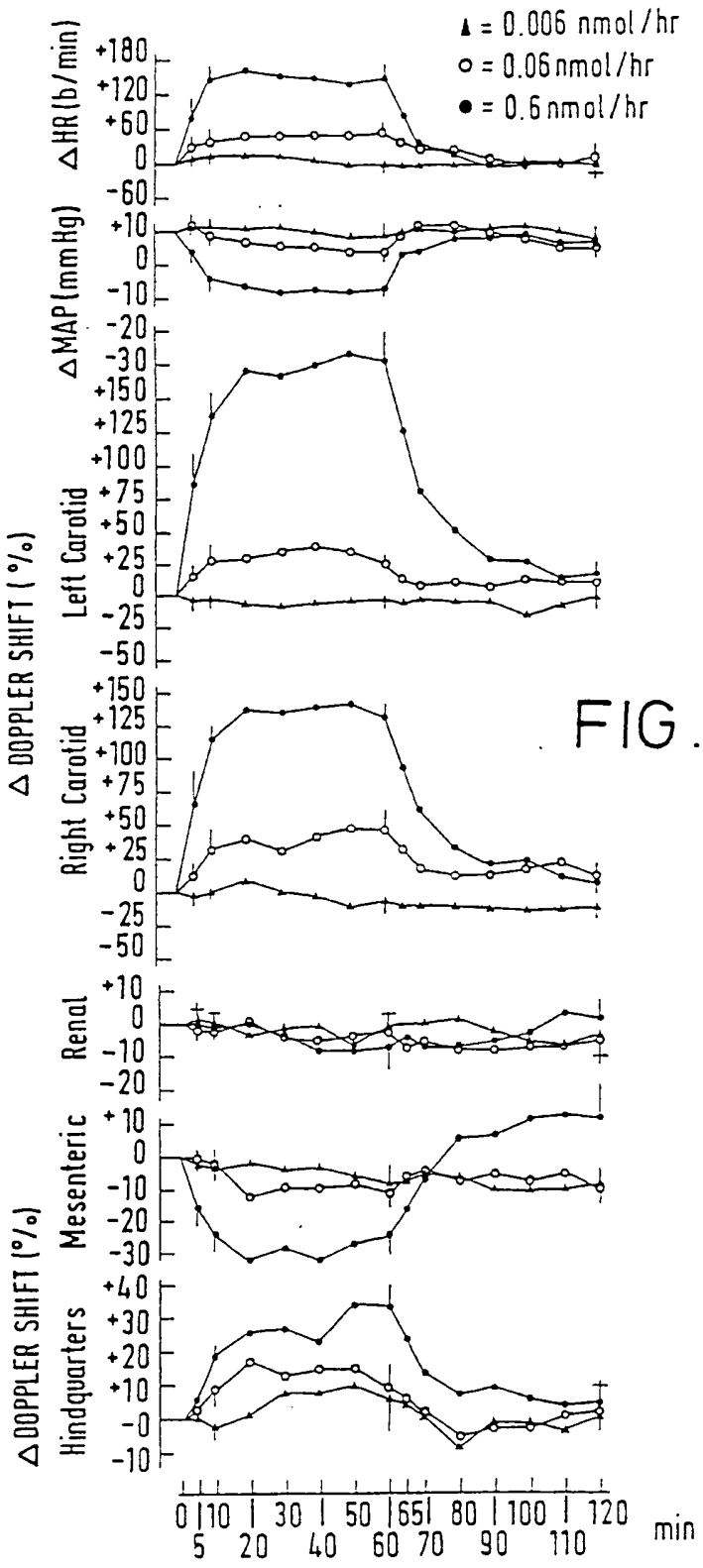

▲ = 0.006 nmol/hr
○ = 0.06 nmol/hr
● = 0.6 nmol/hr
ΔHR (b/min)
+180
+120
+60
0
-60
ΔMAP (mm Hg)
+10
0
-10
-20
-30
Δ DOPPLER SHIFT (%)
Left Carotid
+150
+125
+100
+75
+50
+25
0
-25
-50
Right Carotid
+150
+125
+100
+75
+50
+25
0
-25
-50
Renal
+10
0
-10
-20
Δ DOPPLER SHIFT (%)
Mesenteric
+10
0
-10
-20
-30
Hindquarters
+40
+30
+20
+10
-0
-10
0 10 30 50 65 80 100 120 min
5 20 40 60 70 90 110

FIG. 13

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 88/00877

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 37/02; C 07 K 7/10

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K 37/00; C 07 K 7/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	JPN. J. Pharmacol, volume 43 (suppl.), 1987, I. Ikegaki et al.: "The effect of calcitonin gene-related peptide (CGRP) on cerebrovascular system in dogs", page 96P, abstract 0-132 see the whole abstract --	1-5,7-16
Y	Proc. Natl. Acad. Sci. USA, volume 83, August 1986, J. McCulloch et al.: "Calcitonin gene-related peptide: functional role in cerebrovascular regulation", pages 5731-5735 see abstract; page 5731, "Introduction"; pages 5733-5735, "Discussion" --	1-5,7-16
Y	Neurosurg. Rev., volume 10, no. 3, 1987, Walter de Gruyter & Co., (Berlin, DE), H. Hara et al.: "Perivascular innervation of the cerebral circulation: involvement in the pathophysiology of subarachnoid hemorrhage", pages ./.	1-5,7-16

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12th January 1989	- 8 FEB 1989
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: M. VAN MOL

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	171-179 see abstract; page 171, "Introduction"; pages 174-176, paragraphs 4.2, 6.2. and 6.3 --	
Y	Cephalalgia, volume 6, suppl. 4, 1986, C. Owman: "Multiple transmitter amines and peptides in cerebro-vascular nerves: possible links in migraine pathophysiology", pages 49-62 see page 49; page 50, table 1; page 58, "Concluding remarks" --	1-5,7-16
A	Nature, volume 313, 3 January 1985, S.D. Brain et al.: "Calcitonin gene-related peptide is a potent vasodilator", pages 54-56 see the whole article --------	1-5,7-16

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers ..... because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claim numbers 6,17 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

According to PCT Rule 10.1(e) only such technical terms should be used as are generally accepted in the art. Therefore "H7030" (claim 3) is insufficient for characterization.
Moreover, an "amount" cannot be defined by its pharmacological effects.

Claims 3,8,13,14 searched incompletely.

3. [ ] Claim numbers ..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.